Innovation Tops Current Trends in the 2016 Oncology Drug Pipeline

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Last year witnessed a new high in the number of US Food and Drug Administration (FDA) approvals of new pharmaceuticals, including new molecular entities (NMEs) and new Biologic License Applications (BLAs), amounting to a total of 45 NMEs and BLAs in all disease states compared with 41 approved in 2014 and much fewer (27) in 2013.[1]

Of these 45 NMEs and BLAs entering the market last year, 16 were novel therapies for cancer,[2] providing patients new hope through novel treatment options and new mechanisms of action. New trends in oncology drug development are reflected in the increasing use of biotechnology in the development of anticancer drugs, including immunotherapies or monoclonal antibodies, adoptive-cell therapies, and new vaccines.[3]

Innovation continues to be a much sought-after quality by the FDA in its approval of new drugs to improve patient outcomes, which is reflected in the agency's close work with the pharmaceutical industry. According to the FDA, "Innovation drives progress. When it comes to innovation in the development of new drugs and therapeutic biological products, FDA's Center for Drug Evaluation and Research (CDER) supports the pharmaceutical industry at every step of the process."[2]

Introducing the FDA's summary of its drug approvals in 2015, Janet Woodcock, MD, Director of the FDA's CDER, said, "Each year, CDER approves hundreds of new medications, most of which are variations of previously existing products….However, products in a small subset of these new approvals, that we refer to as novel drugs, are among the more truly innovative products that often help advance clinical care to another level."[1]

Of the 16 new oncolytics approved by the FDA in 2015, the report highlights 9 drugs that were considered truly innovative: "Noteworthy cancer treatments include **Darzalex**, **Empliciti**, **Farydak**, and **Ninlaro**, to treat patients with multiple myeloma…, **Alecensa** and **Tagrisso**, to treat certain patients with non-small cell lung cancer, **Cotellic**, to treat certain patients with metastatic melanoma…, **Lonsurf**, for the treatment of certain patients with metastatic colorectal cancer, and, **Yondelis**, for treatment of soft tissue carcinoma" [emphasis in the original].[1]

These drugs highlight the innovative trends that have characterized the oncology pipeline in recent years, manifested by the many first-in-class drugs entering the market last year and continuing into 2016, and by the drugs representing the first pharmaceuticals approved by the FDA for a specific tumor type. So the oncology pipeline is not showing any signs of slowing down for now. Indeed, according to the new report from the IMS Institute for Healthcare Informatics, the oncology pipeline has expanded by 63% over the past 10 years.[4]

In 2015, the IMS Institute described innovation in the oncology pipeline as focused on combination therapies, biomarkers, and drugs developed for cancer types that have few treatment options.[5] In its new report released on June 1, 2016, it further highlights innovation, saying that "The surge of innovation in cancer treatments is catching the attention of health system stakeholders and participants around the world….The focus on oncology will continue over at least the next five years, driven by unmet needs that remain high, a bulging pipeline of oncology drugs in clinical development, and limited availability in most countries."[4]

Current Trends in the Oncology Pipeline

Clearly, innovation tops the trends in the current oncology pipeline. Another prominent trend is the high cost of cancer drugs, with new drugs entering the market carrying ever-greater costs, as reflected by financial support services offered by many drug manufacturers concomitant to the release of new drugs, in the attempt to mitigate the considerable economic burden on patients who are facing increasing out-of-pocket costs. According to the IMS Institute, the global costs associated with oncology drugs and supportive care medicines increased by 11.5% in 2015, currently reaching $107 billion, projecting that by 2020, global costs for oncology drugs will exceed $150 billion.[5]

This trend in part reflects the high costs of immunotherapies and targeted therapies, which continue to dominate the oncology pipeline, as well as the increasing competition for those drugs among new biotechnology companies that have recently joined the drug development scene, motivated by the increasing success of specialty drugs, which characterize the majority of new oncology drugs in the pipeline. Oral drugs are yet another growing trend that is much more common than even 5

Table 1 Oncology Drugs Approved by the FDA Through May 20, 2016

Drug name	Manufacturer	Indication	Class/Route	Approval date/Comments
Ofatumumab (Arzerra)	Novartis	Recurrent/progressive CLL after ≥2 lines of therapy	CD20-directed cytolytic antibody; IV	*New indication:* January 19, 2016 Priority review
Carfilzomib (Kyprolis)	Amgen	Relpased/refractory multiple myeloma w/ dexamethasone or w/ lenalidomide + dexamethasone	Proteasome inhibitor; IV	*New indication:* January 21, 2016
Nivolumab (Opdivo)	Bristol-Myers Squibb	Unresectable/metastatic melanoma regardless of *BRAF* mutation status, in combination w/ ipilimumab; newly diagnosed advanced melanoma + *BRAF* mutation	PD-1 inhibitor; IV	*New indications:* January 23, 2016 Accelerated approval
		Classic Hodgkin lymphoma after autologous HSCT and posttransplant brentuximab vedotin		May 17, 2016 *(new tumor type)* Accelerated approval; BT; orphan drug
Eribulin mesylate (Halaven)	Eisai	Unresectable/metastatic liposarcoma after anthracycline-containing regimen	Microtubule inhibitor; IV	*New indication (new tumor type):* January 28, 2016 Priority review; orphan drug
Ibrance (palbociclib)	Pfizer	HR+, HER2– advanced/metastatic breast cancer, w/ fulvestrant	CDK4/CDK6 inhibitor; oral	*New indication:* February 19, 2016 BT; priority review
Everolimus (Afinitor)	Novartis	Progressive, well-differentiated NETs of GI/lung origin	mTOR inhibitor; oral	*New indication (new tumor type):* February 26, 2016
Obinutuzumab (Gazyva)	Genentech	Relapsed/refractory follicular lymphoma, w/ bendamustine	CD20-directed cytolytic antibody; IV	*New indication (new tumor type):* February 26, 2016 Priority review
Ibrutinib (Imbruvica)	Pharmacyclics	First-line therapy for CLL	BTK inhibitor; oral	*New indications:* March 4, 2016 First chemotherapy-free first-line treatment
		SLL w/ or w/o 17p deletion		May 9, 2016
Crizotinib (Xalkori)	Pfizer	Metastatic NSCLC + *ROS1* mutation	TKI; oral	*New indication:* March 11, 2016 BT; priority review; orphan drug
Defibrotide sodium (Defitelio)	Jazz Pharmaceuticals	Hepatic veno-occlusive disease w/ renal/pulmonary dysfunction after HSCT	DNA derivative anticoagulant; IV	March 30, 2016: Priority review; orphan drug First drug for this indication
Venetoclax (Venclexta)	AbbVie/ Genentech	CLL w/ 17p deletion for second-line therapy	BCL-2 inhibitor; oral	April 11, 2016: Accelerated approval; BT; priority review; orphan drug First BCL-2 for this indication
Afatinib (Gilotrif)	Boehringer Ingelheim	Metastatic squamous NSCLC	Kinase inhibitor; oral	*New indication:* April 15, 2016
Cabozantinib (Cabometyx)	Exelixis	Advanced RCC	TKI; oral	April 25, 2016: BT; fast track; priority review
Lenvatinib (Lenvima)	Eisai	Advanced RCC, w/ everolimus	TKI; oral	*New indication (new tumor type):* May 13, 2016 BT; priority review
Atezolizumab (Tecentriq)	Genentech	Metastatic urothelial bladder cancer	PD-L1 inhibitor; IV	May 18, 2016: Accelerated approval; BT; priority review First-in-class for this indication

BCL indicates B-cell lymphoma; BT, breakthrough therapy; BTK, Bruton's tyrosine kinase; CDK, cyclin-dependent kinase; CLL, chronic lymphocytic leukemia; GI, gastrointestinal; HSCT, hematopoietic stem-cell transplantation; IV, intravenous; mTOR, mammalian target of rapamycin; NET, neuroendocrine tumor; NSCLC, non–small-cell lung cancer; PD-1, programmed cell death type 1; PD-L1, programmed death ligand 1; RCC, renal-cell carcinoma; SLL, small lymphocytic lymphoma; TKI, tyrosine kinase inhibitor.

years ago, and oral drugs are increasingly making up a larger proportion of the oncology drug costs.[5]

To address the growing concerns surrounding the cost of cancer drugs, various proposals have been made by different experts and other concerned bodies as a means to assess the value of new oncology drugs, by weighing their clinical benefit and contribution to the patient's quality of life versus their costs. Several new value assessment tools were released last year by different organizations, including the American Society of Clinical Oncology's value framework, which was updated in May 2016,[6] and the National Comprehensive Cancer Network's Evidence Blocks.[7]

Other attempts to control drug costs involve proposals to link the cost of a drug to a specific indication, or to the performance of the drug in the real world, but these proposals must be further elucidated and clearly applied to specific therapies or methodologies; it is too soon to assess their value in clinical practice and to the healthcare market as a whole.

The other key trends in the oncology pipeline include expediting the FDA approval using its various pathways, such as priority review and accelerated approval; breakthrough therapy designation (attributed to a drug designed to treat a serious or life-threatening condition); and orphan drug designation (assigned to a drug being developed for a rare type of cancer with <200,000 patients), designations designed to help expedite the development and availability of the drug.

Oncology Drugs Approved Through Late May 2016

Early signs from the first half of 2016 suggest that innovation continues to lead drug development in oncology. By the end of May 2016, the FDA approved 4 novel drugs and 13 new indications in oncology, some of which represent first-in-class therapies (**Table 1**).

The 4 novel drugs include defribotide sodium (Defitelio), the first treatment approved by the FDA for severe hepatic veno-occlusive disease; venetoclax (Venclexta), the first BCL-2 inhibitor to receive FDA approval for chronic lymphocytic leukemia with chromosome 17p deletion; cabozantinib (Cabometyx), a tyrosine kinase inhibitor, approved for advanced renal-cell carcinoma (RCC); and atezolizumab (Tecentriq), the first monoclonal antibody PD-1 ligand 1 inhibitor approved by the FDA for metastatic urothelial bladder cancer (Table 1), a cancer that has not seen a new drug approved by the FDA for more than a decade.

The 2016 Oncology Pipeline

According to the Pharmaceutical Research and Manufacturers of America (PhRMA), as many as 836 drugs and vaccines are currently in various stages of development for cancer; these are either in clinical trials or are awaiting review by the FDA.[8] Of the 836 drugs and vaccines for cancer[8]:

- 123 are for lung cancer (still the leading cause of cancer-related death in the United States)
- 106 for leukemia
- 92 for lymphoma (including non-Hodgkin lymphoma)
- 82 for breast cancer (the leading cancer in US women)
- 58 for brain tumors
- 53 for skin cancer (including melanoma).

Furthermore, approximately 80% of cancer drugs in the current pipeline are potentially first-in-class therapies, and 73% can potentially be classified as personalized medicine, because they target a specific genomic aspect of the tumor, according to PhRMA.[8]

It is not surprising that lung cancer is leading the way in drug development, considering that it remains the leading cause of cancer-related death,[9] despite considerable progress in new therapies. The tumor types leading the pipeline in the number (≥3) of drugs expecting approval in 2016 or are in late-stage development are breast cancer, leukemia, lung cancer, and ovarian cancer (**Table 2**). As shown in Table 2, the majority of these drugs have already received a breakthrough therapy designation, an orphan drug designation, or both, and many are being reviewed under the FDA's various accelerated approval pathways.

Breakthrough therapies and orphan drugs are clearly 2 of the leading trends in the 2016 oncology pipeline, reflecting the continuing efforts of the FDA to encourage the development of potentially life-saving medications to meet unmet needs for specific patient populations.[2] Other promising drugs in late-stage development include drugs for bladder cancer, RCC and other kidney cancers, melanoma, pancreatic cancer, soft-tissue sarcoma, and myelofibrosis (**Table 3**). Although some of these tumor types, especially melanoma, have seen many new drugs approved recently, other tumors, including bladder and brain cancer, have had few or no new drugs in the recent past. As is the case in other tumor types, many of the drugs listed in Table 3 have also received a breakthrough therapy or an orphan drug designation, and are expected to be approved under the FDA's accelerated approval pathways.

Biosimilars: The Future Is Here

The most recent trend in the oncology pipeline involves biosimilars, introduced last year with the FDA approval of filgrastim-sndz (Zarxio), the first biosimilar to receive approval in the United States. This opened the floodgate to a new type of biologic products, which potentially may help control the escalating costs of biologic drugs. As can be expected, the number of biosimilars

Table 2 Drugs in Late-Phase Development for Breast Cancer, Leukemia, Lung Cancer, Ovarian Cancer

Drug name	Manufacturer	Indication	Class/Route	Approval status
Breast cancer				
Abemaciclib	Eli Lilly	Refractory HR+, HER2– advanced/ metastatic breast cancer	CDK4/CDK6 inhibitor; oral	BT: 10/8/2015 Phase 2 trials
Entinostat	Syndax Pharmaceuticals	ER+ breast cancer	Benzamide HDAC inhibitor; oral	BT: 9/11/2013
Glembatumumab vedotin	Celldex Therapeutics	Locally advanced/metastatic triple-negative breast cancer	Fully human monoclonal antibody drug conjugate; IV	Fast track: 5/2010
Neratinib	Puma Biotech	HER2+ breast cancer	TKI; oral	NDA: 2016
Ribociclib (LEE11)	Novartis	HR+, HER2– advanced breast cancer	CDK 4/6 inhibitor; oral	Phase 3 trials
Talazoparib	Medivation	Advanced/metastatic breast cancer + *BRCA* mutation	PARP inhibitor; oral	Phase 3 trials
Veliparib	AbbVie	HER2– metastatic/locally advanced breast cancer + *BRCA* mutation; newly diagnosed triple-negative cancer	PARP inhibitor; oral	Phase 3 trials
Leukemia				
Cytarabine + daunorubicin (Vyxeos)	Celator/Jazz Pharmaceuticals	High-risk (secondary) AML	Nanoscale liposome; IV	Orphan drug: 9/4/2008 Fast track: 1/20/2015 BT: 5/19/2016
Duvelisib	Infinity Pharma	Relapsed/refractory CLL after ≥1 therapies	PI3K inhibitor; oral	Fast track: 8/6/2015
Entospletinib	Gilead	Relapsed/refractory CLL	Syk inhibitor; oral	Phase 2 trials
Inotuzumab ozogamicin	Pfizer	Relapsed/refractory CD22+ ALL	Antibody drug conjugate; IV	BT: 10/19/2015
Midostaurin (PKC412)	Novartis	Newly diagnosed AML + *FLT3* mutation	Multitargeted kinase inhibitor; oral	BT: 2/19/2016
Moxetumomab	AstraZeneca	Hairy-cell leukemia	Anti-CD22 antibody; IV	Orphan drug: 2/4/2016
Pracinostat	MEI Pharma	First-line AML	HDAC inhibitor; oral	Orphan drug: 2/28/2014
Volasertib	Boehringer Ingelheim	First-line AML when intensive induction therapy not an option	PLK-1 inhibitor; IV	BT: 9/17/2013 Phase 3 trials
Lung cancer				
Atezolizumab (Tecentriq)	Genentech	Metastatic/locally advanced NSCLC expressing PD-L1	PD-L1 inhibitor; IV	BLA accepted: 4/11/2016 Priority review PDUFA: 10/19/2016
Avelumab	Pfizer & Merck	NSCLC	PD-L1 inhibitor	Phase 3 trials
BI-1482694	Boehringer Ingelheim	NSCLC + *EGFR T790M* mutation	EGFR TKI; oral	BT: 12/21/2015 PDUFA: 2017
Brigatinib	ARIAD	Advanced NSCLC + *ALK* mutation	ALK inhibitor; oral	BT: 10/1/2014 PDUFA: 2017
Epacadostat	Incyte	NSCLC	IDO1 inhibitor; oral	Phase 2 trials
Rociletinib	Clovis Oncology	NSCLC + *EGFR T790M* mutation	EGFR inhibitor; oral	BT: 5/2015 PDUFA: 6/28/2016
CRLX101	Cerulean Pharma	Relapsed ovarian cancer	Nanoparticle drug conjugate; IV	Orphan drug: 5/26/2015
Ovarian cancer				
Kevetrin	Cellceutix	Ovarian cancer	p53 activator; IV	Orphan drug: 7/15/2015
Niraparib	TESARO	Maintenance therapy for ovarian cancer	PARP inhibitor; oral	Phase 3 trials
Rucaparib	Clovis Oncology	Advanced ovarian cancer + *BRCA* mutation	PARP inhibitor; oral	BT: 4/6/2015
VAL-083	DelMar Pharmaceuticals	Ovarian cancer unlikely to respond to chemotherapy	Bifunctional alkylating agent; oral, IV	Orphan drug: 4/21/2016

ALK indicates anaplastic lymphoma kinase; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BLA, biologics license application; BT, breakthrough therapy; CDK, cyclin-dependent kinase; CLL, chronic lymphocytic leukemia; EGFR, endothelial growth factor receptor; HDAC, histone deacetylase; IDO, indoleamine 2,3-dioxygenase; IV, intravenous; NDA, new drug application; NSCLC, non–small-cell lung cancer; PARP, poly ADP-ribose polymerase; PD-L1, programmed death ligand 1; PDUFA, Prescription Drug User Fee Act; PI3K, phosphatidylinositol 3-kinase; PLK, polio-like kinase; Syk, spleen tyrosine kinase; TKI, tyrosine kinase inhibitor.

Table 3 Drugs in Late-Phase Development for Various Cancers

Drug name	Manufacturer	Indication	Class/Route	Approval status
Bladder cancer				
Durvalumab	AstraZeneca	Urothelial bladder cancer	PD-L1 inhibitor	BT: 2/17/2016
Brain cancer				
VAL-083	DelMar Pharmaceuticals	Medulloblastoma	Bifunctional alkylating agent; oral; IV	Orphan drug: 3/15/2016
Melanoma				
Binimetinib	Array BioPharma	Metastatic melanoma + *NRAS* mutation	MEK inhibitor; oral	Phase 3 trials completed
Encorafenib	Array BioPharma	Melanoma + *BRAF* V600 mutation	BRAF kinase inhibitor; oral	Phase 3 trials
Pancreatic cancer				
Evofosfamide	Threshold Pharmaceuticals	Newly diagnosed metastatic/ unresectable pancreatic cancer, w/ gemcitabine	Hypoxia-activated prodrug; IV	Fast track: 5/12/2015
Kevetrin	Cellceutix Corporation	Pancreatic cancer	p53 activator; IV	Orphan drug: 1/21/2016
Prostate cancer				
Apalutamide	Janssen	Prostate cancer	Androgen receptor antagonist; oral	Phase 3 trials
Rilimogene galvacirepvec/ rilimogene glafolivec (Prostvac)	Bristol-Myers Squibb	Metastatic, castration-resistant prostate cancer	Vaccine	Phase 3 trials
Renal-cell carcinoma				
CRLX101	Cerulean Pharma	Metastatic RCC	Nanoparticle drug conjugate; IV	Fast track: 4/28/2015
Soft-tissue sarcoma				
Olaratumab	Eli Lilly	Advanced soft-tissue sarcoma, in combination w/ doxorubicin	IgG1 monoclonal antibody against PDGFR; IV	Priority review: 5/4/2016 BT; fast track; orphan drug
TRC105	TRACON Pharmaceuticals	Soft-tissue sarcoma	Chimeric anti-CD105 (endoglin) monoclonal antibody; IV	Orphan drug: 1/25/2016
Miscellaneous cancers				
Fostamatinib	Rigel Pharmaceuticals	Chronic immune thrombocytopenic purpura	Syk inhibitor; oral	Orphan drug: 9/8/2015
Momelotinib	Gilead	Myelofibrosis	JAK inhibitor; oral	Orphan drug: 2010 Phase 3 trials
Tazemetostat	Epizyme	Malignant rhabdoid tumors	Histone methyltransferase EZH2 inhibitor; oral	Orphan drug: 2/8/2016
Telotristat etiprate	Lexicon Pharmaceuticals	Carcinoid syndrome, in metastatic NETs	TPH inhibitor; oral	NDA accepted: 5/31/2015 Priority review PDUFA: 11/30/2016

BT indicates breakthrough therapy; EZH, enhancer of zeste homolog; Ig, immunoglobulin; IV, intravenous; JAK, Janus kinase; MEK, mitogen-activated protein kinase; NDA, New Drug Application; NETs, neuroendocrine tumors; PDGFR, platelet-derived growth factor receptor; PD-L1; programmed cell death ligand 1; PDUFA, Prescription Drug User Fee Act; RCC, renal-cell carcinoma; Syk, spleen tyrosine kinase; TPH, tryptophan hydroxylase.

Table 4 Oncology Biosimilars Expecting FDA Approval in 2016

Biosimilar name	Manufacturer	Reference drug	Class/Route	Approval status
Epoetin alfa (Retacrit)	Pfizer	Epogen/Procrit (epoetin alfa)	Erythropoiesis-stimulating agent; SC or IV	BLA filed: 1/2015 PDUFA: 2016
Filgrastim (Grastofil)	Apotex	Neupogen (filgrastim)	Leukocyte growth factor; SC or IV	BLA accepted: 2/13/2015 PDUFA: 2016
Pegfilgrastim	Sandoz	Neulasta (pegfilgrastim)	Leukocyte growth factor; SC	BLA accepted: 11/18/2015 PDUFA: 7/18/2016
Pegfilgrastim	Apotex	Neulasta (pegfilgrastim)	Leukocyte growth factor; SC	BLA accepted: 12/17/2014 PDUFA: 2016

BLA indicates biologics license application; IV, intravenous; PDUFA, Prescription Drug User Fee Act; SC, subcutaneous.

awaiting approval in 2016 is growing. A BLA was filed by the manufacturers of the 4 oncology biosimilars currently in line to receive FDA approval, and 3 of those applications have been accepted by the FDA (**Table 4**).

The FDA has issued several guidance documents outlining the process of approval of biosimilars and the exact nature of biosimilarity (as opposed to interchangeability), but lack of clarity about this new drug category remains. In March 2016, the FDA released its most recent guidance, titled "Labeling for Biosimilar Products," which provides additional clarity. "The goal of a biosimilar product development program is to demonstrate biosimilarity between the proposed product and the reference product, not to independently establish safety and effectiveness of the proposed product. A demonstration of biosimilarity means, among other things, that FDA has determined that there are no clinically meaningful differences between the proposed product and the reference product in terms of safety, purity, and potency," the guidance states.[10]

Furthermore, the label of a biosimilar should not include any data from clinical trials related to the biosimilar, because such studies are not designed to demonstrate efficacy and safety but rather biosimilarity to the reference drug, that is, to "support a demonstration that there are no clinically meaningful differences between the proposed biosimilar product and the reference product for the approved indications."[10] For this reason, the drug label should include information from the clinical trials of the reference drug.[10] At the end of this guidance, the FDA advises it will provide further clarification on interchangeability of a biosimilar in a future guidance.

Conclusion: Are We Closer to a Cure?

Talk about a cure for cancer is in the air, but the evidence remains elusive. Despite President Obama's Moonshot to cancer last year, and despite the enormous progress in cancer drug development and the actual cure available for some cancers, cancer-related deaths are still the second leading cause of death in this country.[9] Nevertheless, the intense rate of innovation in cancer drugs gives one hope that a major breakthrough is not too far away.

A potential turning point in drug development, if not in cancer care itself, may be the introduction, by several pharmaceutical companies, of patient-reported outcomes and patient input as a new component in drug development, with the goal of producing more user-friendly medicines that deliver reduced toxicity and increased convenience, which can improve adherence and outcomes. Could including the patient's voice in drug development, and potentially in drug approval, help to change the drug development paradigm toward a cure? Innovation in the oncology pipeline is thriving, and new scientific discoveries abound. The risk for cancer has no boundaries of any sort. Therefore, the incentive for cure cannot be measured only by financial rewards. ■

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